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JOHANNSEN, DIANA B	
ART UNIT	PAPER NUMBER
1634	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/826,581	ANDERSSON ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *14-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3,10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Search Results* .

DETAILED ACTION

1. The Preliminary Amendment filed December 14, 2001, paper no. 7, has been entered. It is noted that the paper copy of the Sequence Listing filed with paper no. 7 has been entered into the specification after the abstract, in accordance with 37 CFR 1.77(b) (see also *MPEP* 608.01(a)). The computer readable form of the Sequence Listing filed with paper no. 7 has also been entered.

Election/Restriction

2. Applicant's election without traverse of Group I, claims 1-13, in Paper No. 12 is acknowledged.

3. Claims 14-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Priority

4. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

An application data sheet was not filed with the instant application, and the first sentence of the specification does not refer to provisional application 60/195,665. It is noted that Applicant indicated in the transmittal letter of April 5, 2001 that the instant application claims the benefit of provisional application 60/195,665, filed April 7, 2000.

A claim to the provisional application is also indicated in the Declaration that was filed December 14, 2002.

5. If applicant desires priority under 35 U.S.C. 119(e) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

If the application is a utility or plant application filed on or after November 29, 2000, any claim for priority must be made during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2) and (a)(5). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) a surcharge under 37 CFR 1.17(t), and (2) a statement that the entire delay

between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional. The petition should be directed to the Office of Petitions, Box DAC, Assistant Commissioner for Patents, Washington, DC 20231.

6. It is noted that the claimed invention is disclosed in provisional application 60/195,665. Accordingly, Applicants will be entitled to an effective filing date of April 7, 2000 upon perfecting their priority claim as set forth above. Currently, the effective filing date of the claims is the filing date of the instant application, i.e., **April 5, 2001**. (See *MPEP* 201.11 for a further discussion of the requirements for receiving benefit of the filing date of an earlier filed provisional application.)

Information Disclosure Statement

7. The information disclosure statements submitted on June 29, 2001 (paper no. 3) and March 13, 2002 (paper no. 10) have been entered and considered. Initialed and signed copies of the PTO-1449s provided with paper nos. 3 and 10 have been provided with this Office action. Regarding the PTO-1449 of paper no. 3, it is noted that the examiner has provided additional identifying information for the first 3 cited "Other Documents" listed by Applicant (specifically, author and date information have been added to Applicants' citations). Applicant is requested to review the information added by the examiner.

Sequence Identifiers

8. The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a) and (a)(2). However, the specification fails to comply with one or more of the requirements of 37 CFR § 1.821 through 1.825 because the disclosure and the drawings recite sequences that lack description by the appropriate sequence identifier set forth in the "Sequence Listing" as required by 37 CFR § 1.821(d). See, for example, Figures 1-5, pages 3-4, 13, and 17. Appropriate corrections for compliance are required. With regard to Figures 1-5, it is noted that Applicant may either file substitute Figures that recite the appropriate sequence identifiers, or amend the Brief Description of the Figures so as to set forth said sequence identifiers. See *MPEP* 2422.02.

Specification

9. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see, e.g., p. 2). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

10. The use of the trademarks QIAamp®, Wizard®, and A.S.A.P.™ have been noted in this application. These trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112, first paragraph

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 6-7, 9-10, and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to isolated nucleic acid molecules "comprising a human PRKAG3 sequence, wherein said human PRKAG3 sequence comprises a nucleotide sequence variant and nucleotides flanking said sequence variant, and wherein said isolated nucleic acid is at least 15 base pairs in length." Claim 6 requires that the nucleotide sequence variant be an exon 3 variant that "comprises a substitution of a guanine for a cytosine at nucleotide 230." Claim 7 requires that the nucleotide sequence variant be an exon 4 variant that "comprises a substitution of a thymine for a cytosine at nucleotide 550." Claim 9 is drawn to a molecule in which the nucleotide sequence variant is in an intron, while claim 10 further requires that the variant is in intron 6. Claim 12 requires that the PRKAG3 sequence "encodes an AMP-activated protein kinase γ3 subunit polypeptide" that comprises an "alanine residue for a proline residue at amino acid 71." With regard to claim 7, it is further noted that as the teachings of the specification indicate that the exon 4 variant comprising a T for a C is actually at nucleotide 559 (not at "nucleotide 550"), the claim is treated in this rejection

as encompassing the variant disclosed in the specification (C559T) (see, e.g., p. 4, and Table 4). Regarding claim 12, it is noted that the nucleotide sequence variant of claim 6 (C230G) encodes the amino acid variant of claim 12 (see, e.g., Table 4 of the specification).

The specification discloses that PRKAG3 encodes the γ3 subunit of human AMP-activated protein kinase, a protein known to play a role in "regulating the energy metabolism in the eukaryotic cell" (see specification p. 1). The specification provides both the coding sequence (Figure 5; SEQ ID NO: 5) and the genomic sequence (Figures 1-4; SEQ ID NOS 1-4) of PRKAG3. The specification teaches that variations in PRKAG3 "may be associated with metabolic diseases such as diabetes and obesity" (p. 2). Applicants disclose 4 particular polymorphisms in PRKAG3: a polymorphism in exon 3, C230G (wherein 230 refers to the position of the polymorphism in the PRKAG3 coding sequence of SEQ ID NO: 5), a polymorphism in exon 4, C559T (wherein 559 refers to the position of the polymorphism in SEQ ID NO: 5), a polymorphism in exon 10, C1037T (wherein 1037 refers to the position of the polymorphism in SEQ ID NO: 5), and a polymorphism in intron 6, G642C (wherein 642 refers to the position of the polymorphism in the portion of the genomic PRKAG3 sequence set forth in SEQ ID NO: 3). The specification discloses that the C559T polymorphism is silent, while the C230G polymorphism results in the substitution of an alanine for a proline at amino acid 71 of the γ3 subunit, and the C1037T polymorphism results in the substitution of a tryptophan for an arginine at amino acid 340. The specification asserts that the nucleic

acid molecules of the invention are useful in a variety of methods of detecting variants of PRKAG3 associated with metabolic disorders (e.g., as probes or primers [see p. 6-9 of the specification], and in nucleic acid arrays [see p. 12]), and in the production of polypeptides that may be used to prepare antibodies, which antibodies may be used to detect protein variants of the γ3 subunit associated with metabolic disorders (see, e.g., p. 9-11).

It is unpredictable as to whether one of skill in the art could make and use the claimed invention. The specification provides evidence that the C1037T polymorphism occurs more frequently in diabetics than in non-diabetic subjects (see Example 1, particularly p. 16-17; see also paragraph 13, below). Accordingly, given this guidance and the high level of skill of one of skill in the art, the teachings of the specification are sufficient to enable a skilled artisan to use nucleic acid molecules capable of specifically detecting this polymorphism in, e.g., methods of diagnosing diabetes. However, the present claims are limited to molecules comprising the three other polymorphisms described in the specification (C230G, C559T, and the G642C polymorphism of intron 6). The evidence provided in the specification (specifically, in Example 1) does not indicate that the 3 other polymorphisms disclosed by applicants were found to be associated with diabetes, with obesity, or with any other metabolic disorder. Regarding the C230G polymorphism, the specification further discloses that this polymorphism encodes the substitution of an alanine for a proline at amino acid 71 of the γ3 subunit of human AMP-activated protein kinase. Applicants assert that a molecule encoding this polypeptide variant could be used in, e.g., preparation of antibodies that would be useful

in detection of metabolic disorders (see p. 9-11). However, this particular polypeptide has not been characterized. The manner in which the variant polypeptide might function is unknown, and the data provided by applicant does not indicate that this variant polypeptide is found more often in those suffering from diabetes, obesity, or other metabolic disorders. Regarding the silent C559T polymorphism and the G642C intron 6 polymorphism, the specification asserts that such polymorphisms may "alter regulation of transcription as well as mRNA stability" (p. 4). It is well known to those of skill in the art that such polymorphisms may in fact affect mRNA stability, RNA splicing, etc., such that either protein levels or protein structure and/or activity may be affected. However, in the instant case, the disclosure provides no evidence as to whether these 2 polymorphisms do or do not alter mRNA stability, transcription, splicing, etc. Further, as noted above, the data provided in the specification does not support applicants' assertion of a disease association for any of these 3 polymorphisms. It is further noted that the instant claims as written are extremely broad. The claims embrace not only PRKAG3 sequences including the recited polymorphisms, but further encompass nucleic acid molecules comprising such PRKAG3 sequences (i.e., molecules in which sequences flanking the "PRKAG3 sequence" have no relationship to PRKAG3). The claims do not include any sort of functional requirement for the claimed nucleic acids (e.g., a requirement that the claimed molecules specifically detect a PRKAG3 variant sequence known to be associated with disease), and as the claims encompass molecules as few as 15 base pairs in length, the claims as written would encompass, e.g., a 5mer or a 10mer of a PRKAG3 sequence including one of the recited variants,

flanked by unrelated sequences. As the teachings of the specification do not establish a relationship between the 3 polymorphisms encompassed by the instant claims, as discussed above, the guidance in the specification is insufficient to enable one of skill in the art to use any of the large number of molecules encompassed by the claims in the manner asserted by Applicants.

Absent guidance from the specification, one of skill in the art may look to the teachings of the prior art for guidance and enablement of a claimed invention. However, in the instant case, the prior art is silent with respect to the C230G, C559T, and G642C polymorphisms. While one of skill in the art could perform further experimentation to determine the manner in which these 3 polymorphisms affect PRKAG3 mRNA and protein structure or function, and to assay, e.g., additional populations for possible associations with metabolic disorders, the outcome of such experiments cannot be predicted, and it is further unpredictable as to whether any quantity of experimentation would be sufficient to enable one of skill in the art to employ the claimed nucleic acids in methods of detecting metabolic disorders, as asserted by applicants. Accordingly, given the lack of guidance in the specification and in the prior art, the level of experimentation required to make and use the claimed invention is clearly undue. With further regard to claim 7, it is again noted that the claim recites nucleotide "550," whereas the data provided in applicants' specification pertain to nucleotide 559. The prior art is silent with respect to such a polymorphism at nucleotide 550. Accordingly, to the extent that the claim may have been intended to encompass nucleotide 550, neither the specification nor the art provide evidence of an association

of such a molecule with any metabolic disease or disorder. Accordingly, it is unpredictable as to whether such molecules could be used in the manner asserted by applicants, and it would require undue experimentation for one of skill in the art to make and use the claimed invention.

13. Claims 1-5, 8, and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a) isolated nucleic acid molecules consisting of SEQ ID NO: 3 or SEQ ID NO: 5 but including the exon 10 C1037T polymorphism described in the specification, as well as b) isolated nucleic acid molecules consisting of fragments of the molecules of a) that include this polymorphism and that specifically detect PRKAG3 nucleic acids that include the C1037T polymorphism, and for c) isolated nucleic acid molecules comprising a) or b), above, wherein said molecules specifically detect PRKAG3 nucleic acids that include the C1037T polymorphism, does not reasonably provide enablement for isolated nucleic acid molecules "comprising a human PRKAG3 sequence" that comprise any "nucleotide sequence variant," as set forth in the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to isolated nucleic acid molecules "comprising a human PRKAG3 sequence, wherein said human PRKAG3 sequence comprises a nucleotide sequence variant and nucleotides flanking said sequence variant, and wherein said isolated nucleic acid is at least 15 base pairs in length." Claims 2-3 require that "said nucleotide sequence variant is associated with a metabolic disease," and claim 3 further

requires that "said metabolic disease is diabetes or obesity." Claims 4-5 and 8 require that "said nucleotide sequence variant is in an exon." Claim 5 further requires that "said exon is selected from the group consisting of exon 3, exon 4, and exon 10," while claim 8 is drawn to a molecule having a variation in exon 10 that comprises "a substitution of a thymine for a cytosine at nucleotide 1037." Claim 11 requires that the PRKAG3 sequence "encodes an AMP-activated protein kinase γ3 subunit polypeptide" that comprises any "amino acid sequence variant."

The specification discloses that PRKAG3 encodes the γ3 subunit of human AMP-activated protein kinase, a protein known to play a role in "regulating the energy metabolism in the eukaryotic cell" (see specification p. 1). The specification provides both the coding sequence (Figure 5; SEQ ID NO: 5) and the genomic sequence (Figures 1-4; SEQ ID NOS 1-4) of PRKAG3. The specification teaches that variations in PRKAG3 "may be associated with metabolic diseases such as diabetes and obesity" (p. 2). Applicants disclose 4 particular polymorphisms in PRKAG3: a polymorphism in exon 3, C230G (wherein 230 refers to the position of the polymorphism in the PRKAG3 coding sequence of SEQ ID NO: 5), a polymorphism in exon 4, C559T (wherein 559 refers to the position of the polymorphism in SEQ ID NO: 5), a polymorphism in exon 10, C1037T (wherein 1037 refers to the position of the polymorphism in SEQ ID NO: 5), and a polymorphism in intron 6, G642C (wherein 642 refers to the position of the polymorphism in the portion of the genomic PRKAG3 sequence set forth in SEQ ID NO: 3). The specification discloses that the C559T polymorphism is silent, while the C230G polymorphism results in the substitution of an alanine for a proline at amino acid 71 of

the γ3 subunit, and the C1037T polymorphism results in the substitution of a tryptophan for an arginine at amino acid 340. The specification asserts that the nucleic acid molecules of the invention are useful in a variety of methods of detecting variants of PRKAG3 associated with metabolic disorders (e.g., as probes or primers [see p. 6-9 of the specification], and in nucleic acid arrays [see p. 12]), and in the production of polypeptides that may be used to prepare antibodies, which antibodies may be used to detect protein variants of the γ3 subunit associated with metabolic disorders (see, e.g., p. 9-11).

It is unpredictable as to whether one of skill in the art could make and use Applicants' invention in a manner reasonably commensurate with the claims. The specification provides evidence that the C1037T polymorphism occurs more frequently in diabetics than in non-diabetic subjects (see Example 1, particularly p. 16-17). Accordingly, given this guidance and the high level of skill of one of skill in the art, the teachings of the specification are sufficient to enable a skilled artisan to use nucleic acid molecules capable of specifically detecting this polymorphism in, e.g., methods of diagnosing diabetes. However, the evidence provided in the specification (specifically, in Example 1) does not indicate that the 3 other polymorphisms disclosed by applicants were found to be associated with diabetes, with obesity, or with any other metabolic disorder. As discussed in paragraph 12, above, the teachings of the specification do not enable one of skill in the art to use nucleic acids including any of these 3 polymorphisms. Further, while the specification exemplifies 4 particular polymorphisms found in PRKAG3, the instant claims are sufficiently broad so as to encompass <u>any</u>

variant of PRKAG3. Additionally, the claims embrace not only PRKAG3 sequences including any type of variant, but further encompass nucleic acid molecules comprising such PRKAG3 sequences (i.e., molecules in which sequences flanking the "PRKAG3 sequence" have no relationship to PRKAG3). The claims do not include any sort of functional requirement for the claimed nucleic acids (e.g., a requirement that the claimed molecules specifically detect a PRKAG3 variant sequence known to be associated with disease), and as the claims encompass molecules as few as 15 base pairs in length, the claims as written would encompass, e.g., a 5mer or a 10mer of a PRKAG3 sequence including a variant, flanked by unrelated sequences. Thus, while the specification exemplifies a few particular variants of PRKAG3, one of which is shown to be related to diabetes, the claims as written are sufficiently broad so as to encompass thousands of different nucleic acid molecules, most of which would not be useful in the diagnostic methods described in the specification. Thus, while the teachings of the specification would enable one of skill in the art to use isolated nucleic acid molecules that specifically detect PRKAG3 sequences including the C1037T polymorphism, the guidance provided by the specification is insufficient to allow one of skill in the art to use the invention as now claimed.

Absent guidance from the specification, one of skill in the art may look to the teachings of the prior art for guidance and enablement of a claimed invention. In the instant case, the prior art as exemplified by Waterston discloses the genomic sequence of PRKAG3 (GenBank Accession No. AC009974 [3/2001]). The prior art as exemplified by Cheung et al (The Biochemical Journal 346(Pt. 3):659-669 [March 2000]) discloses

the complete coding sequence of PRKAG3 (see Figure 2). The molecule of Cheung et al is a variant of the PRKAG3 coding sequence disclosed by Applicants that includes variations in exons 4, 12 and 13 as compared to the PRKAG3 coding sequence disclosed by applicants (see paragraphs 17 and 18, below). However, neither Waterston nor Cheung et al disclose the particular polymorphisms described in the specification, and the references are silent with respect to any other polymorphisms or variations of PRKAG3 that are associated with a metabolic disease. It is particularly noted that Cheung et al do not indicate that their PRKAG3 molecule may be detected as an indicator of a metabolic disease such as diabetes or obesity. Thus, while their molecule could be used in synthesis of a γ3 subunit of AMP-activated protein kinase, one of skill in the art would not expect that this molecule would be useful in the methods of disease detection described in Applicants' specification. Further, it is well known to those of skill in the art that many genes contain sequence polymorphisms that have no association with any disease. While it is well within the ability of one of skill in the art to conduct further experimentation in order to detect additional PRKAG3 polymorphisms and to further assay those polymorphisms for a possible relationship with disease, it is unpredictable as to whether additional PRKAG3 polymorphisms might be found, as to what those polymorphisms might be, and as to whether those polymorphisms might have any association with diabetes, obesity, or any other metabolic disorder. Given this unpredictability, and particularly as it is unknown as to whether additional PRKAG3 polymorphisms even exist, it is unknown as to whether any quantity of experimentation would be sufficient to enable one of skill in the art to use any molecules other than

molecules capable of specifically detecting the C1037T polymorphism of PRKAG3 in the manner asserted by Applicants. Accordingly, the level of experimentation required to make and use the claimed invention in a manner commensurate in scope with the claims is clearly undue. While the teachings of the specification and of the art would enable one of skill in the art to make and use a) isolated nucleic acid molecules consisting of SEQ ID NO: 3 or SEQ ID NO: 5 but including the exon 10 C1037T polymorphism described in the specification, as well as b) isolated nucleic acid molecules consisting of fragments of the molecules of a) that include this polymorphism and that specifically detect PRKAG3 nucleic acids that include the C1037T polymorphism, and c) isolated nucleic acid molecules comprising a) or b), above, wherein said molecules specifically detect PRKAG3 nucleic acids that include the C1037T polymorphism, it would require undue experimentation for one of skill in the art to make and use Applicants' invention in a manner reasonably commensurate with the instant claims. Regarding claim 8, it is further noted that while the claim recites a particular variation/substitution, the claim as written is sufficiently broad so as to encompass numerous molecules that would not be expected to specifically detect a PRKAG3 sequence including the polymorphism. For example, the claim encompasses molecules thousands of base pairs in length that comprise, e.g., 3 nucleotides of PRKAG3 that include the C1037T polymorphism. Accordingly, it would require undue experimentation to make and use the invention of claim 8 as now claimed. Regarding claim 11, it is further noted that while the claim encompasses nucleic acids encoding a PRKAG3 polypeptide, and nucleic acids including the polymorphism that is shown in the

specification to be associated with diabetes (i.e., nucleic acids encoding the R340W substitution), the claim as written further encompasses PRKAG3 polypeptides containing any amino acid substitution, as well as polypeptides comprising any "amino acid sequence variant" molecule. Such amino acid substitutions result from polymorphisms at the nucleic acid level, and as discussed above, it is unpredictable as to whether additional PRKAG3 polymorphisms might be found, as to what those polymorphisms might be, and as to whether those polymorphisms might have any association with diabetes, obesity, or any other metabolic disorder. Given this unpredictability, and particularly as it is unknown as to whether additional PRKAG3 polymorphisms even exist, it is unknown as to whether any quantity of experimentation would be sufficient to enable one of skill in the art to use the invention as claimed. Accordingly, the level of experimentation required to make and use the invention of claim 11 in a manner reasonable commensurate with the claim is undue.

Claim Rejections - 35 USC § 112, second paragraph

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 6-8 and 11-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is indefinite over the recitation of the limitation "said exon 3 variant." There is insufficient antecedent basis for this limitation in the claims.

Claim 7 is indefinite over the recitation of the limitation "said exon 4 variant." There is insufficient antecedent basis for this limitation in the claims.

Claim 8 is indefinite over the recitation of the limitation "said exon 10 variant." There is insufficient antecedent basis for this limitation in the claims.

Claims 6-8 are indefinite over the recitation of the phrases "a substitution of a guanine for a cytosine at nucleotide 230" (claim 6), "a substitution of a thymine for a cytosine at nucleotide 550" (claim 7), and "a substitution of a thymine for a cytosine at nucleotide 1037" (claim 8). It is unclear as to whether the numbers 230, 550, and 1037 are intended to refer to the location of substitutions in the claimed "isolated nucleic acid molecule," in a particular SEQ ID NO, in the recited exon (e.g., exon 3, exon 4, or exon 10), in the PRKAG3 genomic sequence or coding sequence, etc. Accordingly, the claims do not make clear what particular substitutions are intended to be encompassed thereby. With further respect to claim 7, it is noted that while the claim recites "nucleotide 550," the specification refers to nucleotide 559 at, e.g., p. 4, and in Table 4. Further, nucleotide 550 of preferred SEQ ID NO: 5 is a guanine. Accordingly, it appears that the claim may have been intended to be drawn to a substitution at nucleotide 559. Clarification is required.

Claims 11-13 are indefinite over the recitation of the limitation "said PRKAG3 nucleic acid sequence" in claim 11. There is insufficient antecedent basis for this limitation in the claims. This rejection could be overcome by amending claim 11 to recite "said PRKAG3 sequence."

Claims 12-13 are indefinite over the recitation "wherein said amino acid sequence variant comprises substitution of an alanine residue for a proline residue at amino acid 71" in claim 12 and "wherein said amino acid sequence variant comprises substitution of a tryptophan residue for an arginine residue at amino acid 340" in claim 13. With respect to the term "nucleotide sequence variant," it is noted that the specification makes clear at, e.g., p. 4, that this terminology is intended to refer to variations or alterations in a nucleic acid molecule with respect to wild-type sequence, and not to, e.g., whole molecules that are considered to be "variants." As a limiting definition for the term "amino acid sequence variant" is not provided in the specification, this terminology, as employed in claims 11-13, is sufficiently broad so as to encompass both molecules that are considered to be variants, and particular substitutions/variations within a sequence. As claims 12-13 do not refer to amino acids 71 and 340 of a particular SEQ ID NO or of a particular coding sequence or polypeptide, it is unclear as to whether the claims are intended to be limited to nucleic acid molecules in which the PRKAG3 sequence encodes variations of the particular amino acids of the PRKAG3 polypeptide disclosed in the specification (i.e., in which codons 71/340 of the PRKAG3 coding sequence are altered), or whether the claims are intended to also encompass, e.g., nucleic acids encoding PRKAG3 polypeptides, wherein those polypeptides further comprise any type of "amino acid sequence variant" molecule that includes the substitutions recited in claims 12-13. The claims should be amended so as to clearly apprise one of skill in the art of the structural requirements of the molecules encompassed by the claims.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 1 and 4-5 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Cheung et al (The Biochemical Journal 346(Pt. 3):659-669 [March 2000]).

It is noted that if Applicants perfect their priority claim to provisional application 60/195,665 as discussed above, the Cheung et al reference will constitute prior art under 35 USC 102(a) rather than 35 USC 102(b) (see *MPEP* 706.02(b) and paragraph 6, above).

Claim 1 is drawn to an "isolated nucleic acid comprising a human PRKAG3 sequence, wherein said human PRKAG3 sequence comprises a nucleotide sequence variant and nucleotides flanking said sequence variant, and wherein said isolated nucleic acid is at least 15 base pairs in length." Claim 4 further requires that "said nucleotide sequence variant is in an exon," and claim 5 additional requires that "said exon is selected from the group consisting of exon 3, exon 4, and exon 10." It is noted that the genomic sequence of PRKAG3 is provided in Figures 1-4 of the specification (with Figures 1-4 corresponding to SEQ ID Nos 1-4, respectively), and that the complete coding sequence of PRKAG3 is provided in Figure 5 of the specification (corresponding to SEQ ID NO: 5). It is further noted that "PRKAG3" is an art-recognized term for the

gene encoding the γ3 subunit of human AMP-activated protein kinase, as disclosed at, e.g., page 1 of the specification.

Cheung et al disclose a coding sequence for the γ3 subunit of human AMP-activated protein kinase (see entire reference, particularly Figure 2). It is an inherent property of the nucleic acid molecule disclosed by Cheung et al that it comprises a human PRKAG3 sequence that comprises several nucleotide sequence variants as compared to the coding sequence disclosed by Applicants. See the alignment of instant SEQ ID NO: 5 with the PRKAG3 coding sequence of Cheung et al, which illustrates differences at nucleotides 583-584, 1286, and 1475 of the coding sequence of SEQ 5 as compared to Cheung et al's coding sequence (see also paragraph 18, below). Cheung et al disclose isolated nucleic acid molecules comprising the PRKAG3 sequence depicted in Figure 2 (see page 660), and these molecules are at least 15 base pairs in length. Regarding claims 4-5, it is noted that positions 583-584 of instant SEQ ID NO: 5 correspond to nucleotides 876-877 of instant SEQ ID NO: 2. Applicants' Figure 2 discloses that nucleotides 876-877 of SEQ ID NO: 2 are located within exon 4 (see Figure 2). It is therefore an inherent property of Cheung et al's molecule that it comprises variants located in exon 4. Accordingly, Cheung et al clearly anticipate claims 1, 4, and 5. Regarding claim 4, it is further noted that nucleotide 1286 of SEQ ID NO: 5 corresponds to nucleotide 310 in Figure 4 (SEQ ID NO: 4), which is located in exon 12, and that nucleotide 1475 of SEQ ID NO: 5 corresponds to nucleotide 842 in Figure 4 (SEQ ID No: 4), which is located in exon 13.

Conclusion

18. Sequence search results are cited to illustrate the differences between the PRKAG3 coding sequence of instant SEQ ID NO: 5 and the PRKAG3 coding sequence of Cheung et al (from Figure 2 of The Biochemical Journal 346(Pt. 3):659-669 [March 2000]; deposited as GenEmbl Accession No. AJ249977). In the alignment, the ATG start codon and TGA stop codon are indicated with brackets, and variations are circled.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
December 2, 2002